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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/541,596 | 04/25/2006 | Bradley Paul Morgan | 10444.0090-00000 | 2514 |

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FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
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| EXAMINER | |
|---|---|
| CHANDRAKUMAR, NIZAL S | |
| **ART UNIT** | **PAPER NUMBER** |
| 1625 | |
| **MAIL DATE** | **DELIVERY MODE** |
| 09/07/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/541,596 | MORGAN ET AL. | |
| | Examiner | Art Unit | |
| | Nizal S. Chandrakumar | 1625 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *30 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3,4,6-8 and 10-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *6-8,10-12 and 25-27* is/are objected to.

8)☒ Claim(s) *1,3,4 and 13-24* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

This application filed 04/25/2006 is a 371 of PCT/US04/01069 01/14/2004 which claims benefit of 60/440,133 01/14/2003 and claims benefit of 60/440,183 01/14/2003 and claims benefit of 60/476,086 06/04/2003 and claims benefit of 60/476,517 06/05/2003 and claims benefit of 60/501,376 09/08/2003.

### *Election/Restrictions*

Applicant's election without traverse the subject matter of Group VI (claim 42), drawn to pharmaceutical formulations containing compounds of the formula I wherein $R^1$ = aryl (i.e., Y=Z=C), in the reply filed on 07/30/2007 is acknowledged. Further, in a telephone conversation with Ms. Lauren Stevens, attorney for the applicant, the applicant agreed to cancel claims 56-65.

Claim 42 is cancelled in the amended claims.

Claims 1, 3, 4, 6-8, 10-27 are pending.

Claims 1, 3, 4, 6-8, 10-27 are examined.

1. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

### *Double Patenting*

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided

the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer.

A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 4, 6-8, 10-27 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-51 of U.S. Patent No. 7176222. Although the conflicting claims are not identical, they are not patentably distinct from each other because the generic Formula I of claim of 51 as well as the description and working Examples of 7176222 encompass the compounds of the instant application.

Claims 1, 3, 4, 6-8, 10-27 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-30 43 and 56-59 of copending Application No. 10890829. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds of the claims of the copending application encompass compounds of the instant case.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Claim Rejections - 35 USC § 112***

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 4, 13-14, 16, 21-23 and dependent claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims contain the phrase "optionally substituted" which is indefinite because it is not clear what the substitutions are.

Claims 1, 13-14, 16, 21-23 and dependent claims are rejected as being indefinite because the claims recite "heteroaryl, heteroaralkyl and heterocyclyl" without pointing out what are the heterocyclic groups.

***Claim Rejections - 35 USC § 112***

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1,3, 4 and 13-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making few of the possible structures of formula I, does not reasonably provide enablement for plethora of possible structures encompassed by the formula I. For instance enablement is provided for one aromatic heterocyclic R2 group (pyridin-3-yl, alkyl-substituted pyridin-3-yl), one substitution for R1.2 (i.e. H) and one R1.3 (i.e.F), one for the variable X (1i.e. O) and two heterocyclyls (pyrrolidinyl or piperidinyl both 3-yls). However the formula I contains several independently varying possibilities (vide infra). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the relevant factual considerations.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)).

1) The breadth of the claims,

2) The nature of the invention,

3) The state of the prior art,

4) The level of one of ordinary skill,

5) The level of predictability in the art,

6) The amount of direction provided by the inventor,

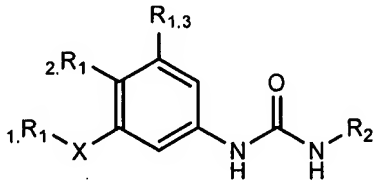
7) The existence of working examples,

8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

While all the above factors were considered, some of the specific considerations are described below:

The nature of the invention: The invention relates to substituted urea derivatives, particularly to compounds that selectively modulate the cardiac sarcomere, and specifically to compounds, pharmaceutical formulations and methods of treatment for systolic heart failure, including congestive heart failure.

The breadth of the claims: The claims are drawn to pharmaceutical formulations containing compounds of the Formula I,




With independently varying variables layered with additional substituents on top of substituents, not to mention the stereo chemical possibilities resulting from substitutions on substitutions, the number of theoretically conceivable compounds for the formula is in billions, rendering the scope of the claims large, one that is not supported by the disclosure in the specification. The claims are also drawn to unknown 'optional substitutions' on top of the substitutions and unknown possibilities for heterocyclic modifications.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the art of medicinal chemistry, it is noted that each embodiment of the invention is required to be

individually assessed for viability.

The amount of direction or guidance present: The direction provided is limited and is amenable to making only few of the possibilities encompassed by the formula I. The direction provided is limited to making only two heterocyclic possibilities for R1.1; H substitution for R1.2; fluoro substitution for R1.3 and pyridin-3-yl for R2. The formation of the aryl-ether linkage either by nucleophilic displacement or by Mitsunobu reaction limits what substitutions are possible for the central aromatic ring. The specification does not adequately discuss potential complications and competing reactions during the processes described. For instance, the art-recognized low-reactivity of 2- and 4-amino groups of 2- and 4-aminopyridines is not discussed in the specification.

When the amines for the urea-formation are available, making of urea is a well-known process that is adequately described in the prior art. However, with respect to the R2 substitution, the specification provides direction for only pyrdin-3-yl amine for the R2 variation.

There is no direction or guidance for making compounds of the formula I wherein X is other than O.

There is no direction or guidance for making compounds of the formula I wherein R1.2 is other than H.

There is no direction or guidance for making compounds wherein R1.3 is other than the halo F.

There is no direction or guidance for making compounds wherein R2 is other than pyridin-3-yl.

The presence or absence of working examples. The working example present in the specification is limited to making compounds of the formula III wherein R1.1 is pyrrolidinyl or piperidinyl (both 3-yl with respect ether linkage), R1.1 is H, R1.3 is F, R2 is pyridin-3yl.

There is no working example for making compounds of the formula I wherein X is other than O.

There is no working example for making compounds of the formula I wherein R1.2 is other than H.

There is no working example for making compounds wherein R1.3 is other than the halo F.

There is no working example for making compounds wherein R2 is other than pyridin-3-yl.

The state and the predictability of the art: The state of the prior art limits whether one could use the

generic schemes provided in the specification for making compounds with all the claimed variables. The state of the art is unpredictable as to functional group compatibility during many chemical transformations, in spite of major advances in protecting group strategies in synthesis. As stated with respect to urea formation, the limiting parameters for this reaction are the availability of the amine partners. The chemistry needed for making heterocyclic amines substituted with functionalities such as halo or ester groups is unpredictable. For instance, the formation of a urea wherein R2 is 3-bromo-piperidin-3-yl is unpredictable because of potential complication of self-reaction of the starting amine. The low and unpredictable reactivity of amino group of many heterocyclic amines towards even highly reactive electrophiles is well recognized in the art. The existence of such unpredictabilities establishes that the contemporary knowledge in the art of organic synthesis would prevent one of ordinary skill in the art from accepting any claimed process for selected molecules such as the ones present in the specification on its face as universally applicable for all the conceivable structures of formula I.

The quantity of experimentation needed: In the instant case, there is a substantial gap between the guidance provided and the breadth of the claims. Given the direction and working Examples provided in the specification, in order to utilize the invention as claimed, the skilled artisan would be presented with an unpredictable amount of experimentation. The guidance provided in the specification is limited. Consequently, a burdensome amount of research would be required by one of ordinary skill in the art to bridge this gap.

In addition, the specification is silent about the biological activity of the compounds of the formula I. One of ordinary skill in the art would have to engage in undue experimentation not only in making the compounds of formula I but also would have to engage in extensive research to identify a compound encompassed by the generic formula I that would have acceptable PK and PK parameters. The instant disclosure is broad and generic and does not support the instant claims.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting

license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

In conclusion, based on the evidence regarding each of the above mentioned Wands factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

The specification provides for the enablement of making compounds of the Formula I wherein,

R1.1 is piperidin-3-yl or pyrrolidin-3-yl

X is O

R1.2 is H

R1.3 is F

R2 is pyridin-3-yl (substituted with either an unsubstituted alkyl group or alkoxy group).

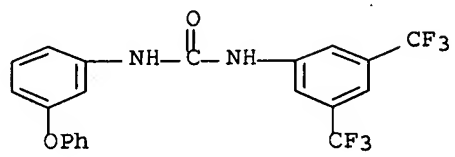
***Claim Rejections - 35 USC § 102***

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

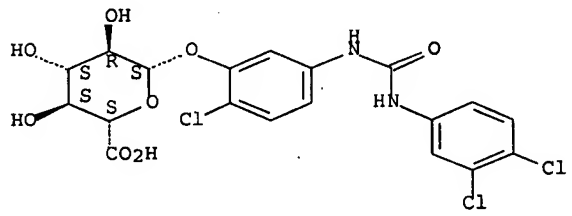
5. Claims 1 and 14-24 are rejected under 35 U.S.C. 102(b) as being anticipated in the prior art as shown below:

J. R. Geigy A.G.(GB 921682) teach



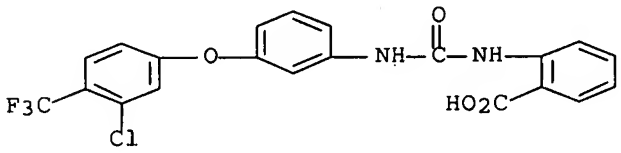
corresponding to compound of formula I wherein R1.1 is aryl; X is O; R1.2 is H; R1.3 is H; R2 is substituted aryl.

Jeffcoat et al. STN Accession number: 1977:462295; Document number: 87:62295 (Drug Metabolism and Disposition (1977), 5(2), 157-66) teach



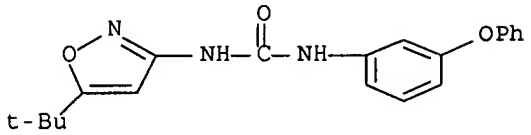
corresponding to compound of formula I wherein R1.1 is heterocyclyl (substituted tetrahydropyranyl); X is O; R1.2 is halo; R1.3 is H; R2 is substituted aryl.

Parg et al (EP 27965) teach



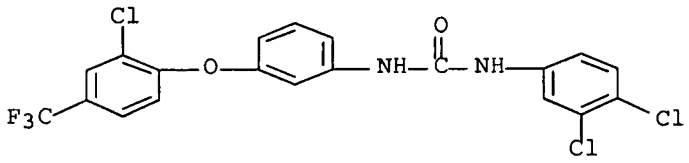
corresponding to compound of formula I wherein R1.1 is substituted aryl X is O; R1.2 is H; R1.3 is H; R2 is substituted aryl.

Dumas et al. (WO 9932106) teach



corresponding to compound of formula I wherein R1.1 is unsubstituted aryl X is O; R1.2 is H; R1.3 is H; R2 is substituted isooxazol-3-yl (for claim 16).

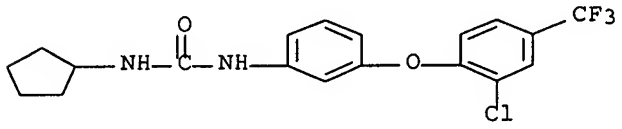
Parg et al (EP 81142)teach



corresponding to compound of formula I wherein R1.1 is substituted aryl X is O; R1.2 is H; R1.3 is H; R2 is halo substituted aryl (for claim 17).

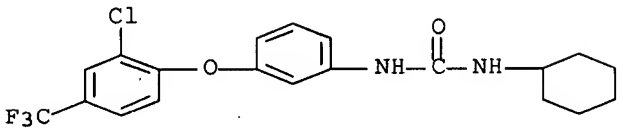
corresponding to compound of formula I wherein R1.1 is substituted aryl; X is O; R1.2 is H; R1.3 is H; R2 is substituted aryl.

Parg et al (EP 81142) teach



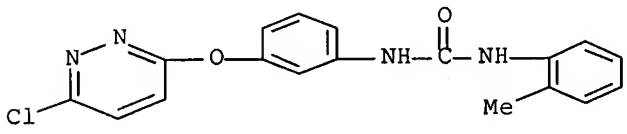
corresponding to compound of formula I wherein R1.1 is substituted aryl X is O; R1.2 is H; R1.3 is H; R2 is cycloalkyl (for claim 21)

Parg et al. (DE 3147879) teach

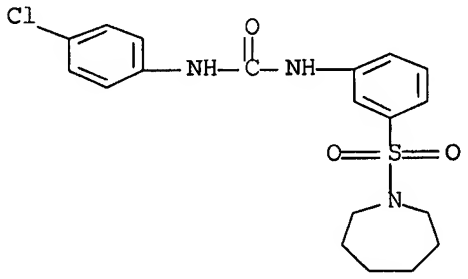


corresponding to compound of formula I wherein R1.1 is substituted aryl X is O; R1.2 is H; R1.3 is H; R2 is cyclohexyl (for claim 24)

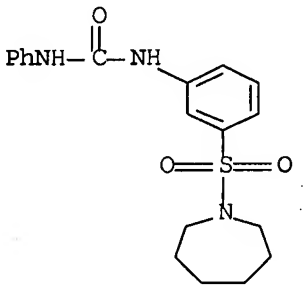
Kempter et al. STN Accession number: 1984:510849; Document number: 101:110849) Hochschule Karl Liebknecht Potsdam (1983), 27(1), 101-20) teach



corresponding to compound of formula I wherein R1.1 is substituted heteroaryl X is O; R1.2 is H; R1.3 is H; R2 is substituted aryl.

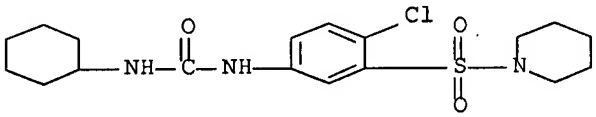


corresponding to compound of formula I wherein R1.1 is heterocyclyl; X is SO2; R1.2 is H; R1.3 is H; R2 is substituted aryl.



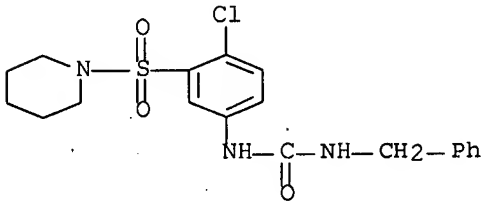
corresponding to compound of formula I wherein R1.1 is heterocyclyl; X is SO2; R1.2 is H; R1.3 is H; R2 is unsubstituted aryl.

El-Sharief et al. (STN Accession number: 1987:549199; Document number: 107:14919) Proceedings of the Indian National Science Academy, Part A: Physical Sciences (1987), 53(1), 179-88) teach

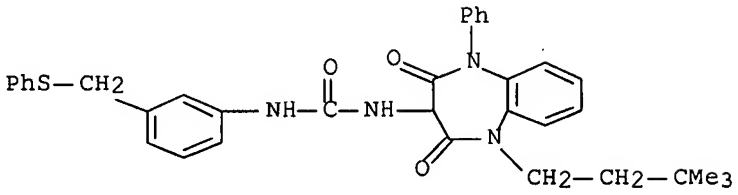


corresponding to compound of formula I wherein R1.1 is heterocyclyl; X is SO2; R1.2 is halo; R1.3 is H; R2 is cycloalkyl.

For claim 22

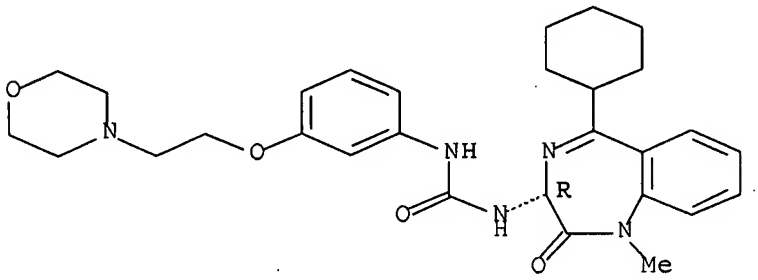


Finch et al. (WO 9314074)teach



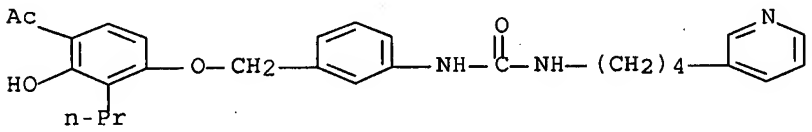
corresponding to compound of formula I wherein R1.1 is aryl X is lower-alkylene-S; R1.2 is H; R1.3 is H; R2 is substituted hetrocyclyl.

Chambers et.al. (US 5556969) teach



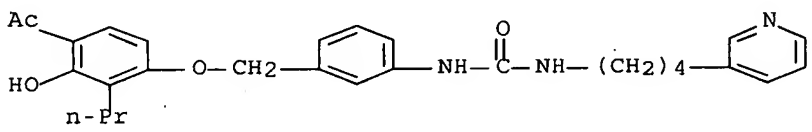
corresponding to compound of formula I wherein R1.1 is hetrocyclyl ;X is lower-alkylene-O; R1.2 is H; R1.3 is H; R2 is substituted hetrocyclyl (claim 21).

Carson et al. (US 4672066) teach



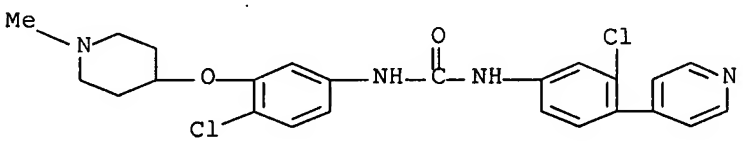
corresponding to compound of formula I wherein R1.1 is substituted aryl ;X is lower-alkylene-O; R1.2 is H; R1.3 is H; R2 is heteroaralkyl (claim 21).

Carson et al. (US 4672066) teach



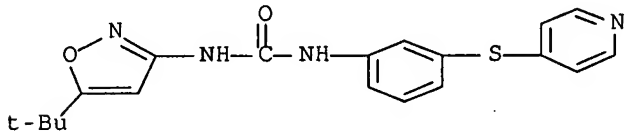
corresponding to compound of formula I wherein R1.1 is hetrocyclyl ;X is lower-alkylene-O; R1.2 is H; R1.3 is H; R2 is W-R2.1, W= alkylene, R2.1 is (pyridiyl) hetrocyclyl (claim 22).

Gaster et al. (WO 9850346) teach



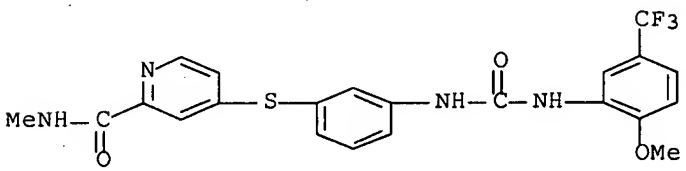
corresponding to compound of formula I wherein R1.1 is hetrocyclyl ;X is O; R1.2 is halo; R1.3 is H; R2 is unsubstituted heteroaryl.

Dumas et al.(WO 9932111)

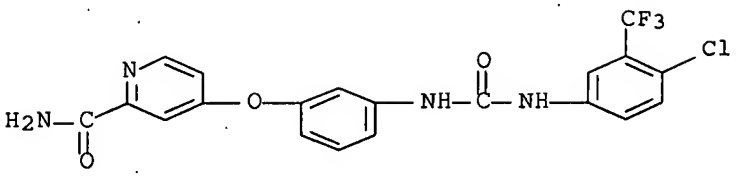


corresponding to compound of formula I wherein R1.1 is substituted heteroaryl (pyridinyl); X is S; R1.2 is H; R1.3 is H; R2 is substituted heteroaryl (oxazole).

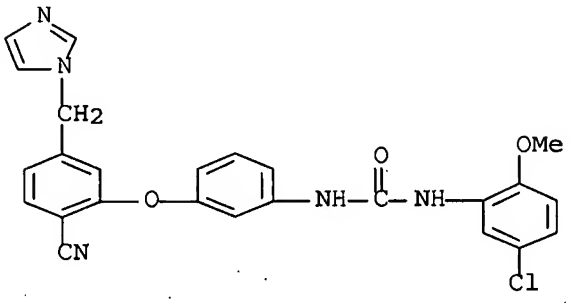
Riedl et al. (WO 2000041698)



corresponding to compound of formula I wherein R1.1 is substituted heteroaryl (pyridinyl); X is S; R1.2 is H; R1.3 is H; R2 is substituted heteroaryl.

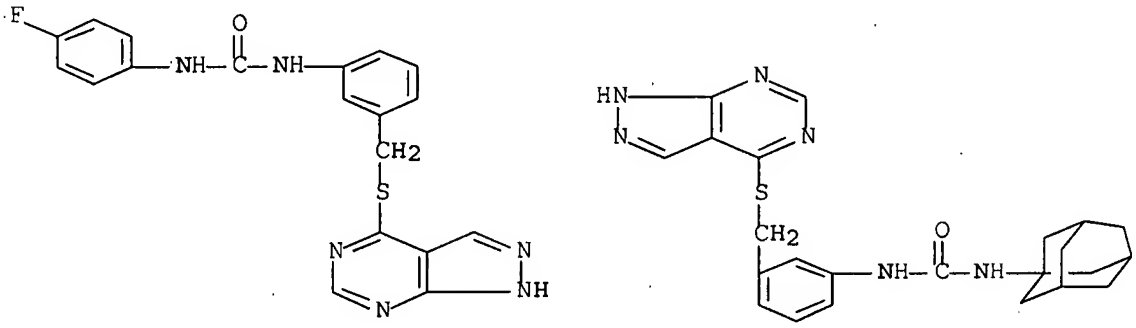


corresponding to compound of formula I wherein R1.1 is substituted heteroaryl (pyridinyl); X is O; R1.2 is H; R1.3 is H; R2 is substituted aryl.



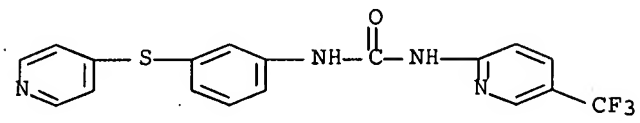
corresponding to compound of formula I wherein R1.1 is substituted aryl ; X is O; R1.2 is H; R1.3 is H; R2 is substituted aryl.

Bender et al. (US 6635641)

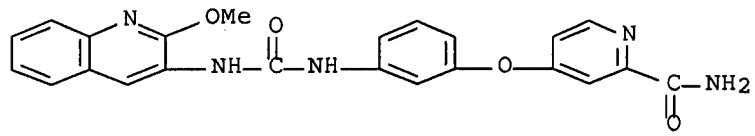


corresponding to compound of formula I wherein R1.1 is unsubstituted heteroaryl ; X is O; R1.2 is H; R1.3 is H; R2 is cycloalkyl .

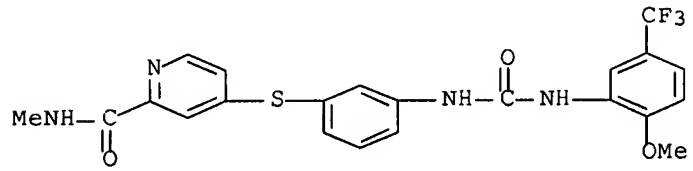
Dumas et al. (US 2002065296)



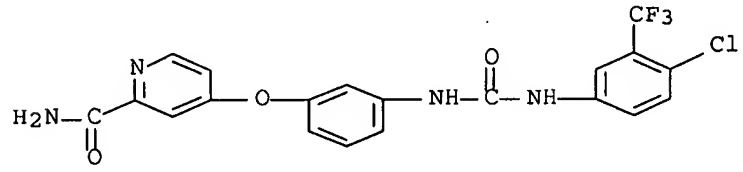
corresponding to compound of formula I wherein R1.1 is unsubstituted heteroaryl ; X is S; R1.2 is H; R1.3 is H; R2 is substituted heteroaryl.



Dumas et al. (WO 2002062763)

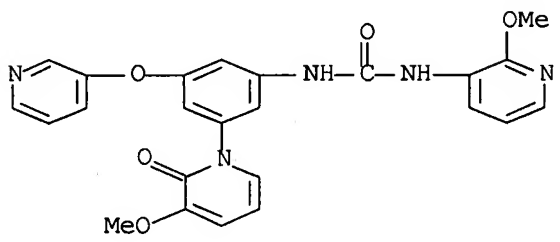


corresponding to compound of formula I wherein R1.1 is substituted heteroaryl ; X is S; R1.2 is H; R1.3 is H; R2 is substituted aryl.



corresponding to compound of formula I wherein R1.1 is substituted heteroaryl ; X is O; R1.2 is H; R1.3 is H; R2 is substituted aryl.

Malik et al. (WO 2003059258, International filing date 12/2/0/2002)) teach



corresponding to compound of formula I wherein R1.1 is substituted heteroaryl ; X is O; R1.2 is H; R1.3 is H; R2 is pyridine-3-yl.

***Allowable Subject Matter***

6. Claims 6-8, 10-12, 25-27 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form, free of double patenting rejections, including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nizal S. Chandrakumar whose telephone number is 517-272-6202. The examiner can normally be reached on 8.30 am – 5 pm Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867 or Primary Examiner D. Margaret Seaman can be reached at 571-272-0694. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the

Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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